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Extra-nodal extension is an important prognostic parameter for both colonic and rectal cancer

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We thank Huang and colleagues [1] for their positive comments on our recent meta-analysis [2], in which we assessed the potential relationship between extra-nodal extension (ENE) of nodal metastasis and prognostic indexes in colorectal cancer. We found consistent evidence that ENE is associated with mortality and recurrence of disease, across multiple sensitivity analyses [2], which remained robust after adjustment for publication bias. Moreover, we conducted meta-regression analyses to explain the low-moderate heterogeneity we encountered (see supplementary table 8) in line with best practice. Nonetheless, Qun et al [1] have proposed two new subgroup analyses using the same data based on geographical location (Europe vs Japan) and site of tumor (colon, rectum, both colon and rectum cancer) to test the robustness of our results. Qun et al replicated all of our findings, except from the all-cause mortality in colon cancer (HR 1.396: 0.848-2.3) and colon and rectum cancer together (HR 1.513: 0.968-2.365).

Although these additional analyses are of potential interest, we respectfully share a number of limitations. First, our initial analyses had low-moderate heterogeneity and our meta-regression analyses already significantly explained large portions of the heterogeneity we encountered. Second, Qun et al did not report any heterogeneity metric in their new analyses, so it is unclear to what extent their additional analyses addressed their own primary concern that our paper found low-moderate heterogeneity. Third, Qun et al included a limited number of studies in each subgroup (only 5 studies reported HR estimates: 2 studies for colon, 2 for rectum and 1 regarding colorectal cancer). Indeed, they only included 5 studies out of the 13 considered in our meta-analysis, thus type II error might be a factor in their null findings. Moreover, the *p* for the interaction for this subgroup analysis is 0.229, suggesting that this factor is not a probable moderator of our findings. Notably, the staging system does not separately consider colon and rectum cancer [2], further justifying our approach. Moreover, the meso-rectal adipose tissue, the main anatomical difference between a surgical specimen of colonic and of rectal cancer, contains very few lymph nodes: also from this point of view (i.e. number of lymph nodes and possible metastasis) colonic and rectal cancer can be studied together. Interestingly, the morphologic aspect most similar to ENE, that is represented by the free tumor deposits in adipose tissue (N1c category), is already considered in TNM staging system for both rectal and colonic cancer. Lastly, in other cancer types ENE appeared as a significant prognostic index [3,4], and also of

importance independently from specific anatomical sub-distinction (e.g. carcinoma of pancreas vs of ampulla of Vater) [5].

In conclusion, we partly agree with the analyses of Qun et al., and are grateful they echo our calls for further research considering the prognostic role of ENE in colorectal cancer. However, we have a number of potential concerns that do not shift our stance, based on the data, that future research should consider colon and rectum cancer as only one entity.

DISCLOSURE

The Authors have declared no conflicts of interest.

REFERENCE

[1] X. Qin, Q. Huang. Prognostic impact of extracapsular lymph node involvement in colorectal cancer. Ann Oncol 2016; [in press].

[2] Veronese N, Nottegar A, Pea A et al. Prognostic impact and implications of extracapsular lymph node involvement in colorectal cancer: a systematic review with meta-analysis. Ann Oncol 2016; 27: 42-48.

[3] Luchini C, Veronese N, Pea A, et al. Extra-nodal extension in N1-adenocarcinoma of pancreas and papilla of Vater: a systematic review and meta-analysis of its prognostic significance. Eur J Gastroenterol Hepatol 2016; 28:205-209.

[4] Luchini C, Nottegar A, Solmi M, et al. Prognostic implications of extra-nodal extension in node-positive squamous cell carcinoma of the vulva: a systematic review and meta-analysis. SurgOncol 2015. September 14 [Epub ahead of print] doi: 10.1016/j.suronc.2015.09.005.

[5] Veronese N, Luchini C, Nottegar A, et al. Prognostic impact and implications of extra-nodal extension in lymph-node positive thyroid cancers: a systematic review and meta-analysis. J Surg Oncol 2015. October 23 [Epub ahead of print] doi: 10.1002/jso.24070.